United States Environmental Protection Agency

# The Virtual Liver Project

*International Science Forum on Computational Toxicology*
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# Multidisciplinary Cross-ORD Team

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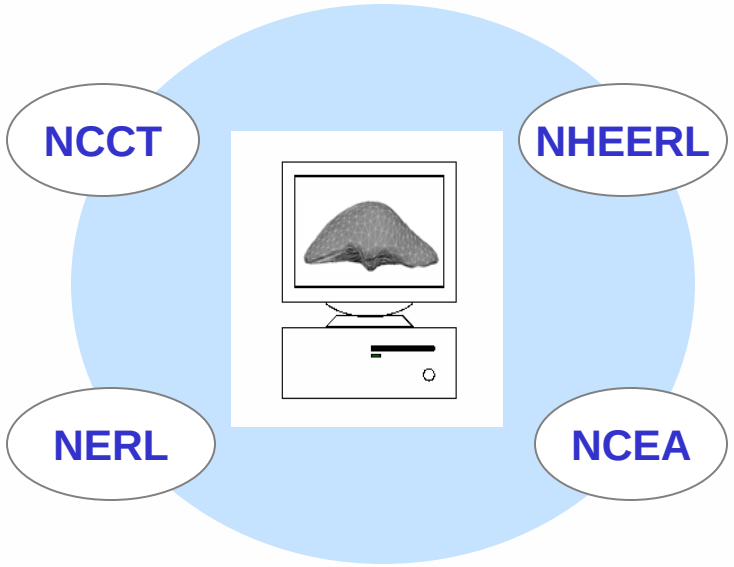


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**Growing …**

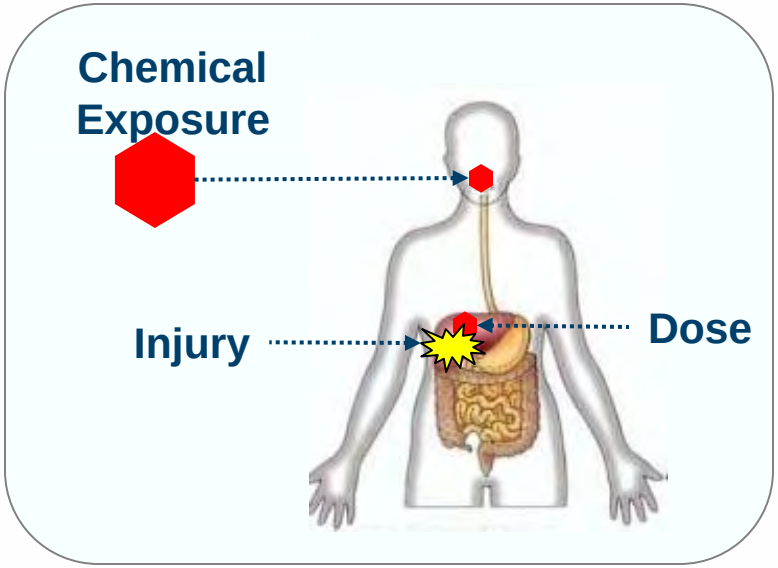
# Outline

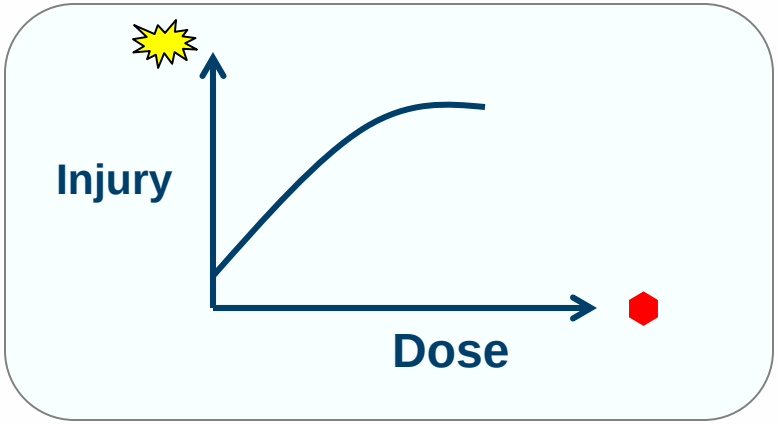
1. Risk assessment challenges
2. Virtual Liver Concept
3. Development approach
4. Initial steps

# Assessing Risk of Environmental Chemicals

*Risk assessment needs:*

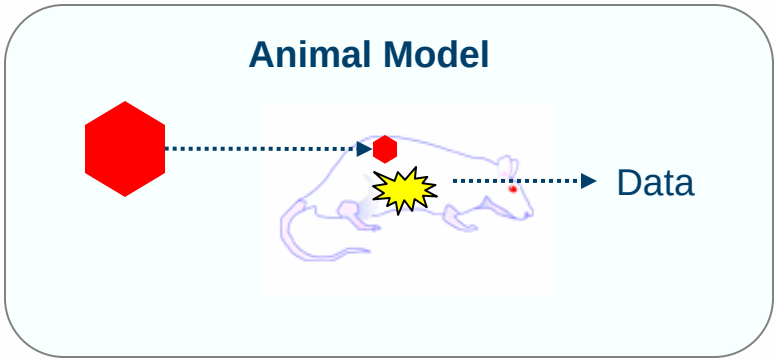
- What is the dose of chemical inside body at a given site?
- How is the chemical metabolized and disposed ?
- Where in the body does the chemical cause injury ?
- How does the injury depend on dose of the chemical ?

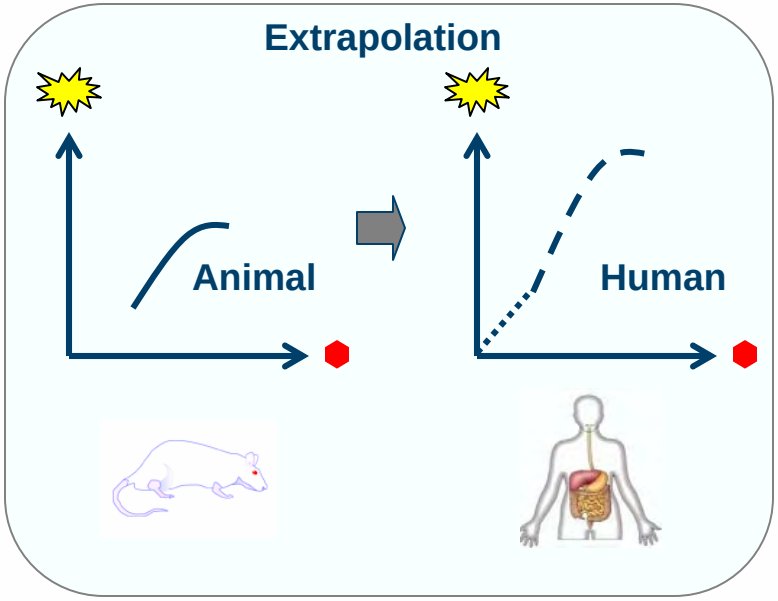


# Risk Assessment Challenges

- Injury is generally measured in laboratory animals
- Animal data is *extrapolated* to predict human dose and injury
- Extrapolation issues:
  - Limited mechanistic knowledge
  - Effect of species on parameters
  - Absence of low dose data
- *Liver is a major target organ for toxicity of chemicals*



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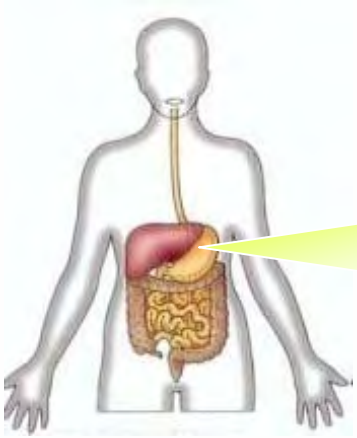
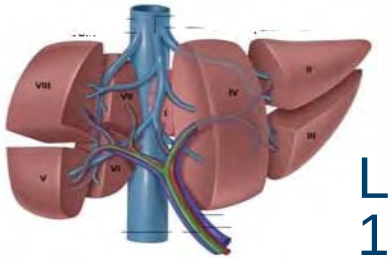
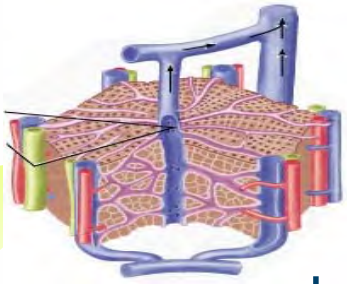
**Liver Function:** multiple levels of biological organization & scales



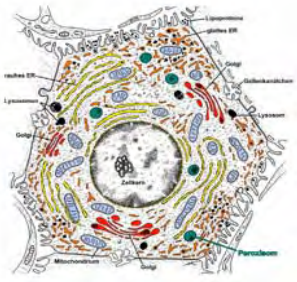
Liver
$10^{-2}$m



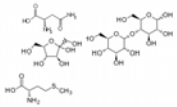
Lobule
$10^{-2}$m

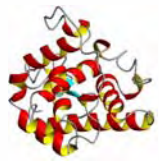


Lobe
$10^{-3}$m



Cell
$10^{-6}$m





Molecules
$10^{-9}$m

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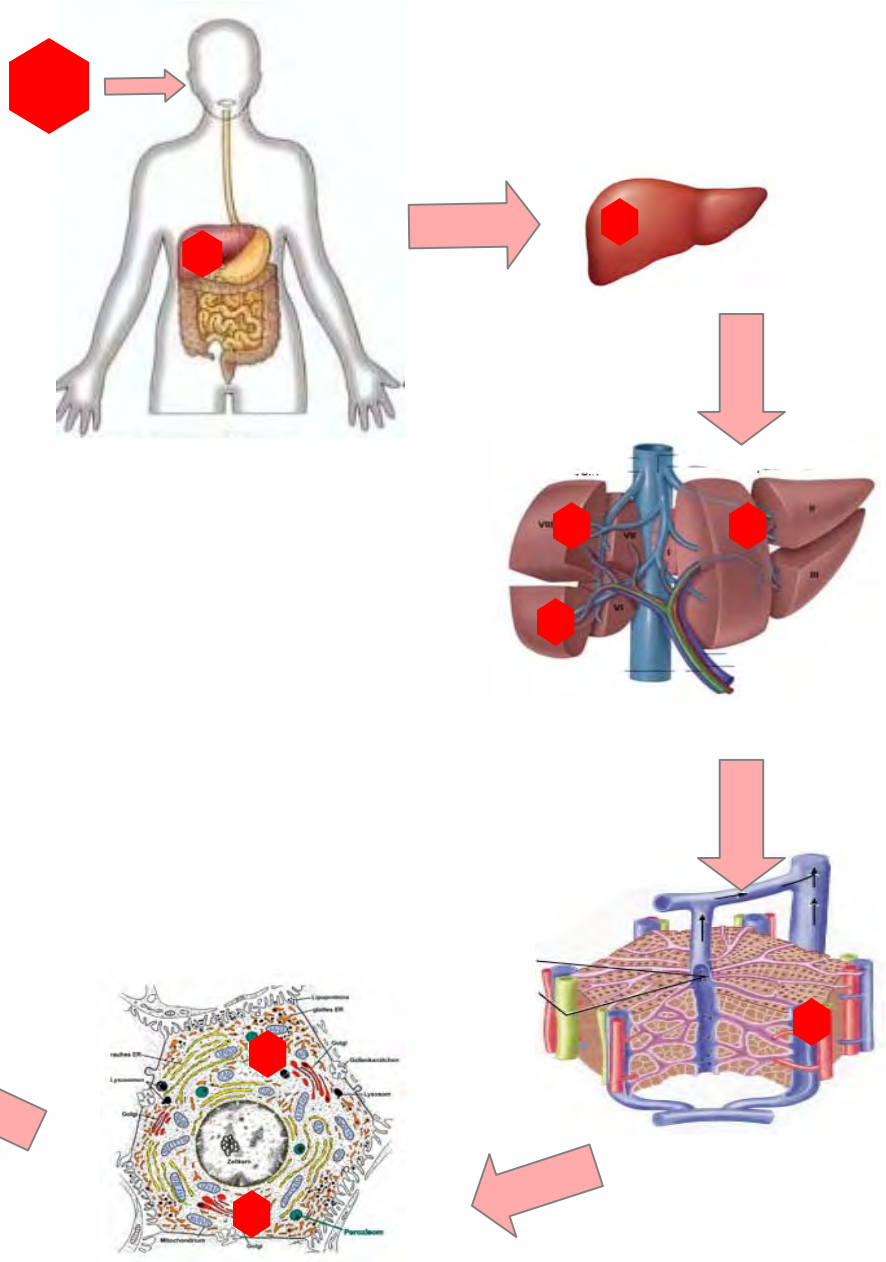
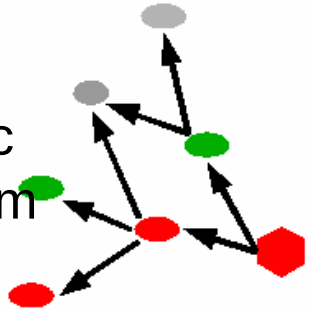
**Biological systems** respond to perturbation with **homeostatic** responses …



E.g. Xenobiotic Metabolism



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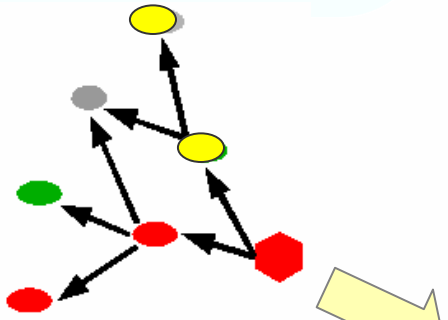
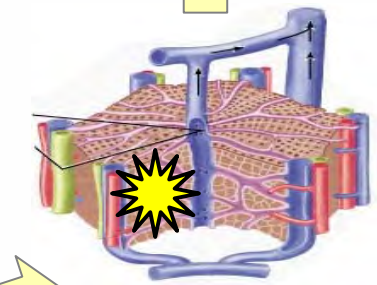
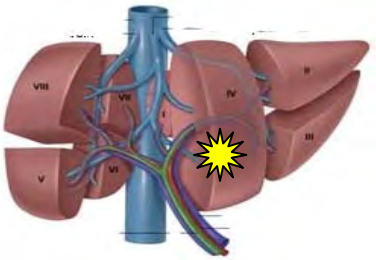
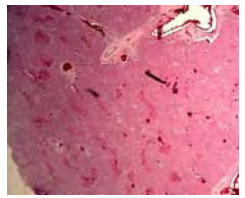
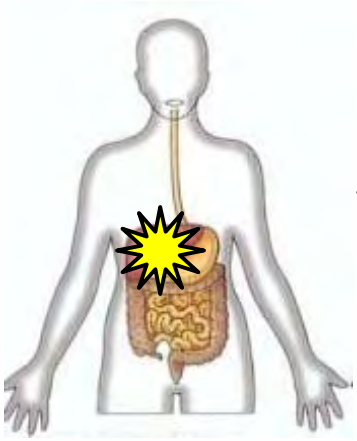
When homeostatic capacity is overcome liver **injury** occurs – triggered by molecular events and manifested later in tissue











# A Computational Liver Model

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## Goals

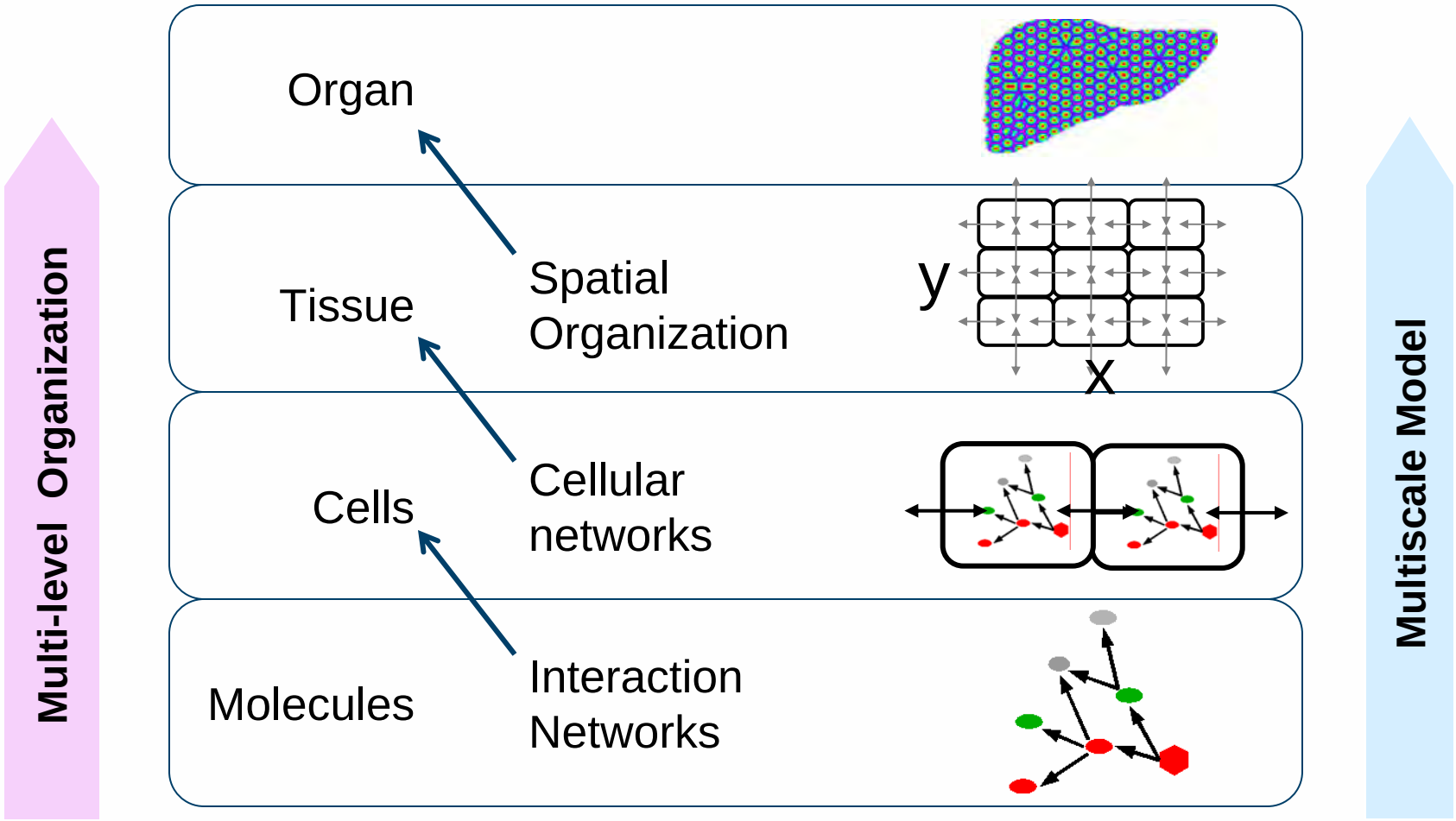
- Aid risk assessment
- Predictive tools to extrapolate response between chemicals, doses, times and species

## Approach

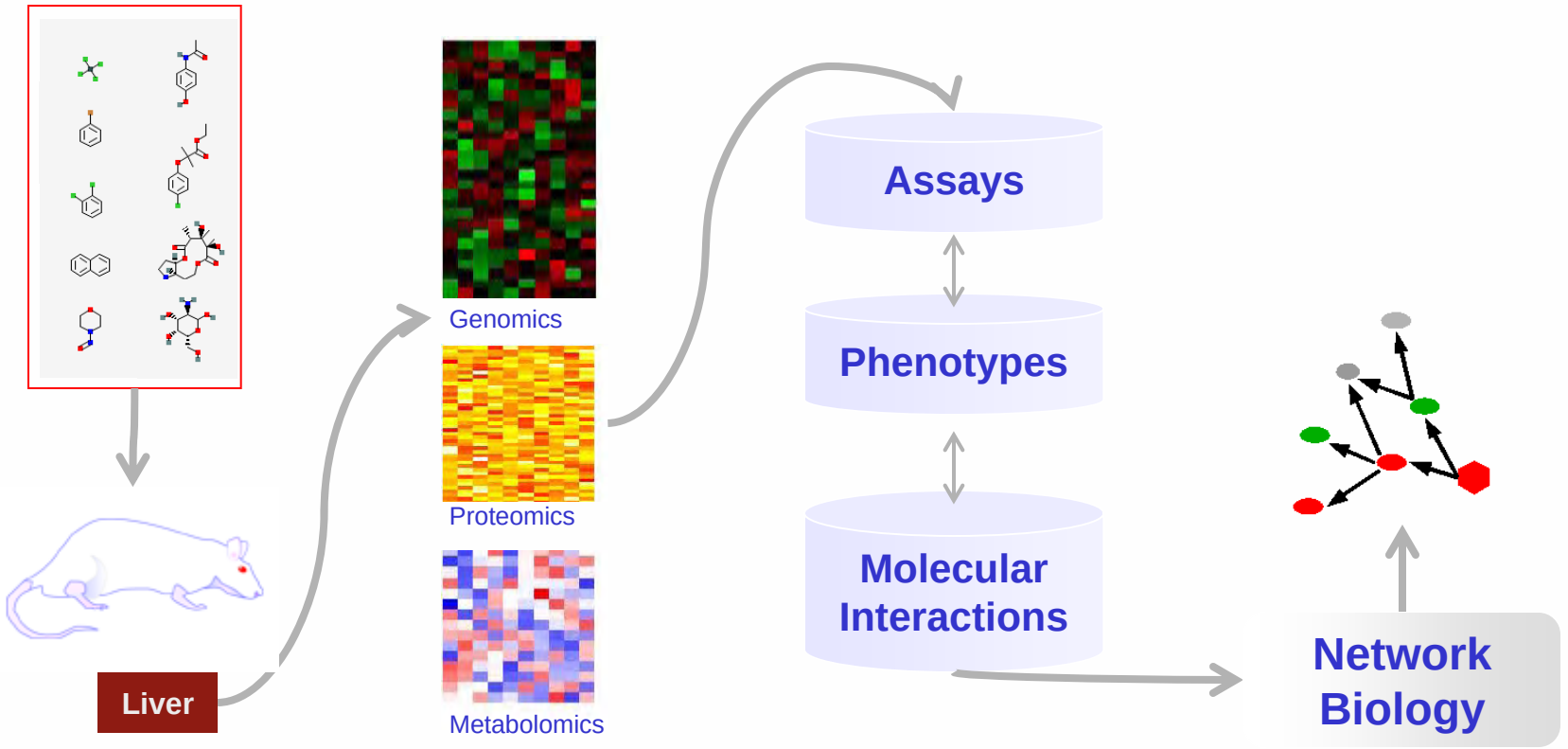
- Encode knowledge at multiple scales of liver function
- Simulate dose-response of environment chemicals

**The Virtual Liver**

# Virtual Liver: Multiscale Model of Liver Organization

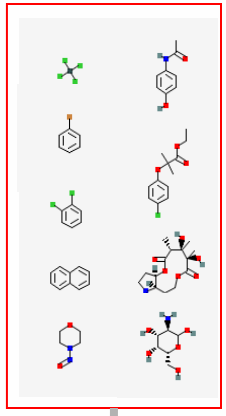


# Molecular Networks: Signaling, Gene-regulation and Metabolism

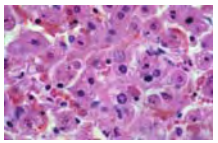



Experiment → *-omic* Assays → Data Integration → Molecular Interactions

# Cellular Networks: Hepatocytes, Kupffer Cells



Liver



Histopath

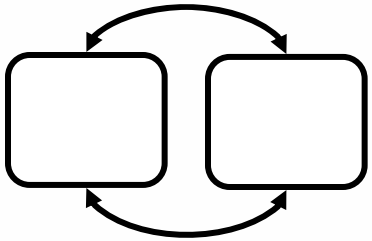
**Cell Fate**
Death
Prolif.

**Cell-cell signaling**

Assays

Phenotypes

Literature



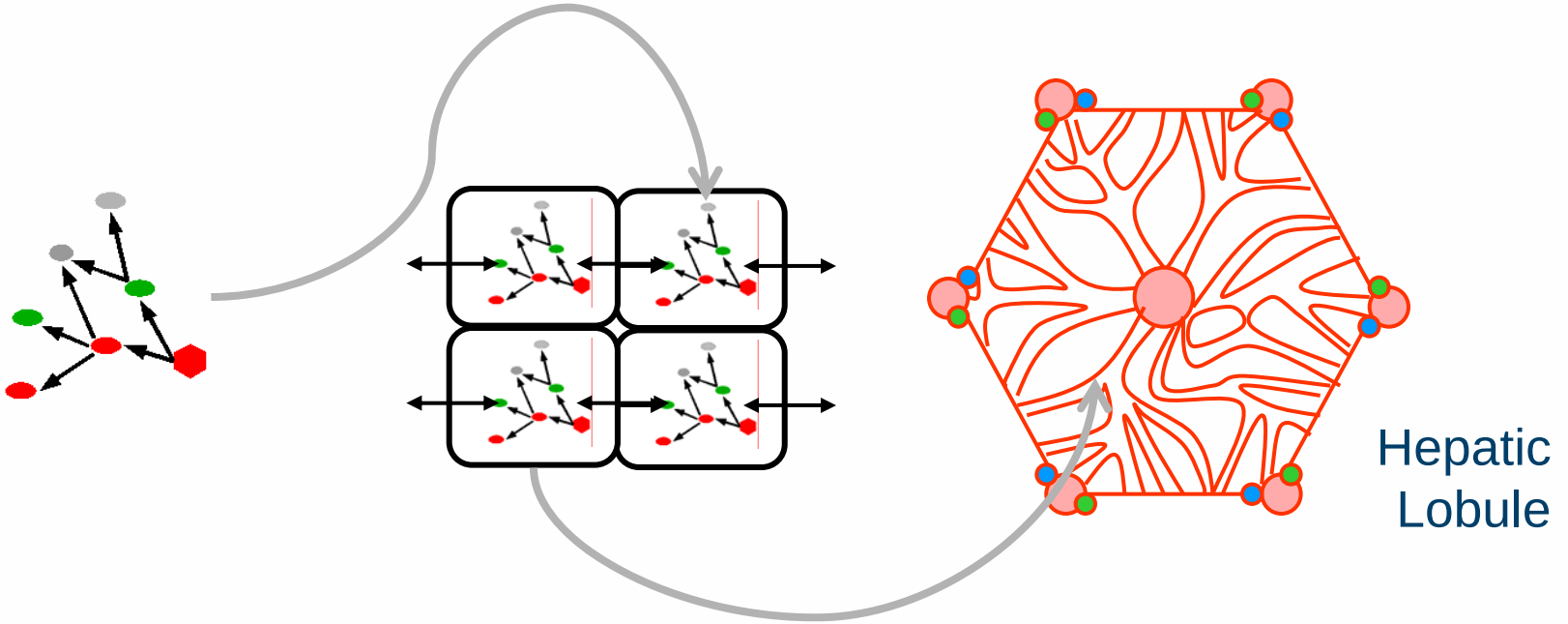
Experiment

Cellular Assays

Data Integration

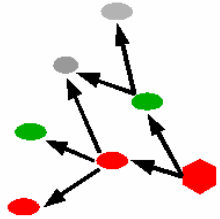
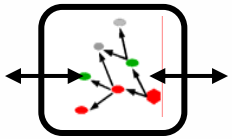
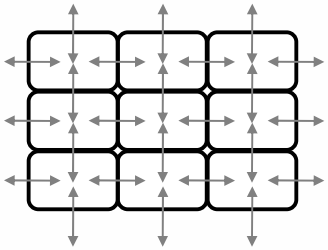
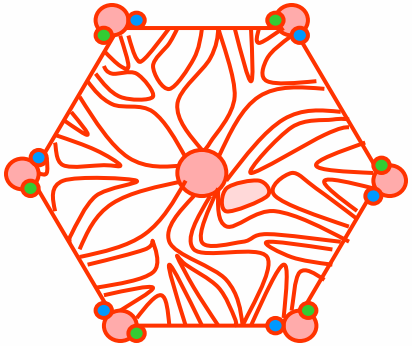
Cellular Interactions

# Multiscale Tissue Model



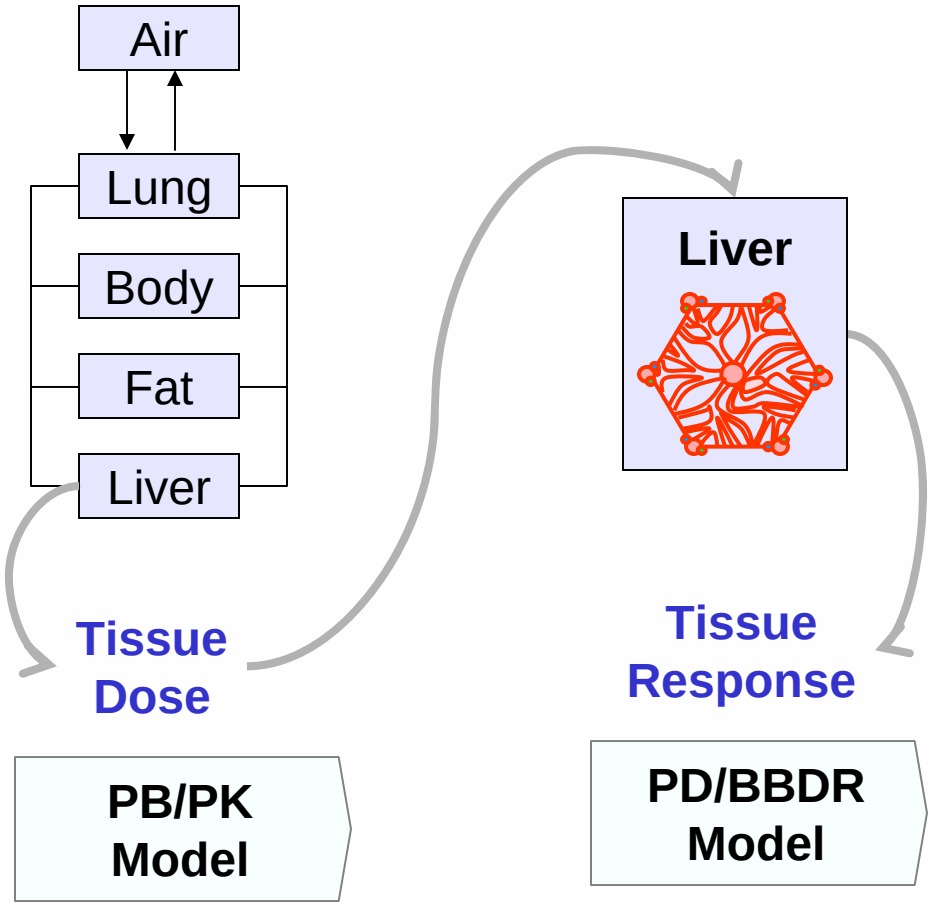

**Molecular Interactions** → **Cellular Interactions** → **Tissue Model**

# Emergent Response

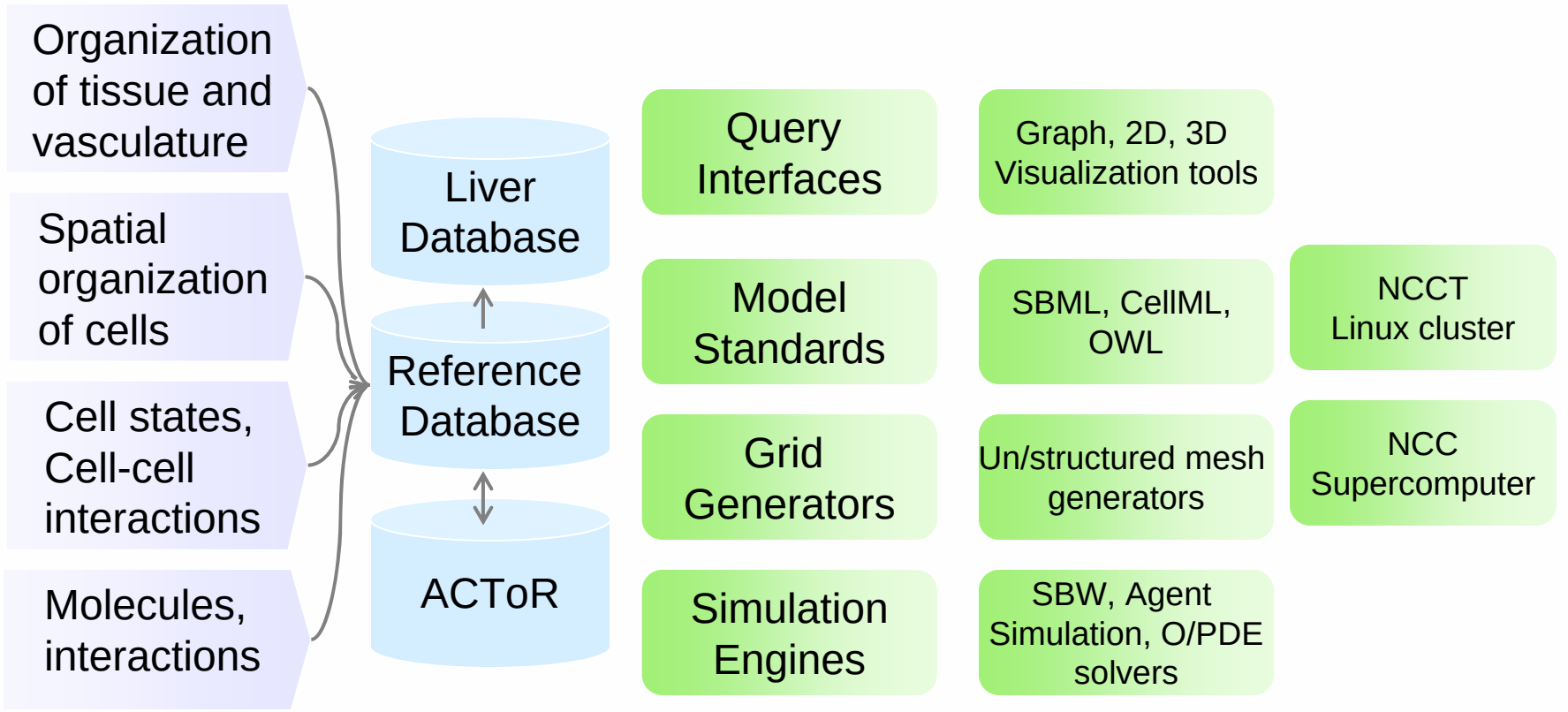





| | | | | |
|---|---|---|---|---|
| **Parts** | Interacting Molecules | Intra/Inter-cellular interactions | Multi-cellular interactions | Tissue & circulation |
| **Response** | Changes in network topology | Changes in cell fate | Changes in morphology | Liver Injury |

# Integrate with Physiological Modeling: PK and BBDR



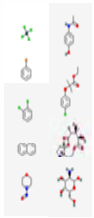
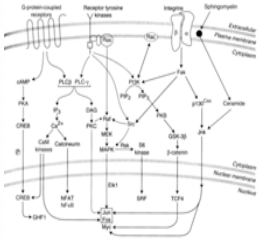
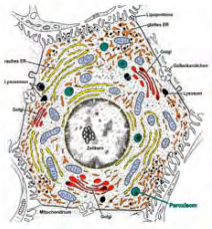
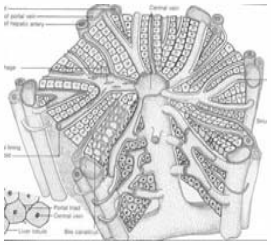
# Virtual Liver Infrastructure: Database, Software Tools & Hardware




**Literature & Repositories** | **Biological Databases** | **Required Tools** | **Community Resources** | **Parallel Computing**

# Initiative on Nuclear Receptor Mediated Chronic Liver Injury

## Collaboration with NHEERL

Environmental Chemicals → Molecular response → Cellular response → Tissue response

**Chemicals**

Pesticides
- Conazoles
- Pyrethroids

Toxics
- DE-71
- PCBs
- Phthalates
- PFAA/PFOA

**Molecular Response (Early)**

| NR-sig | Gene-reg. | Transcription |
|---|---|---|
| CAR | *cis*-reg. | Xen. Met. |
| PXR | *Trans*-reg. | Phase I |
| AhR | | |
| LXR | | Phase II |
| FXR | | |
| PPARα | | Phase III |

**Cell fate**

Proliferation

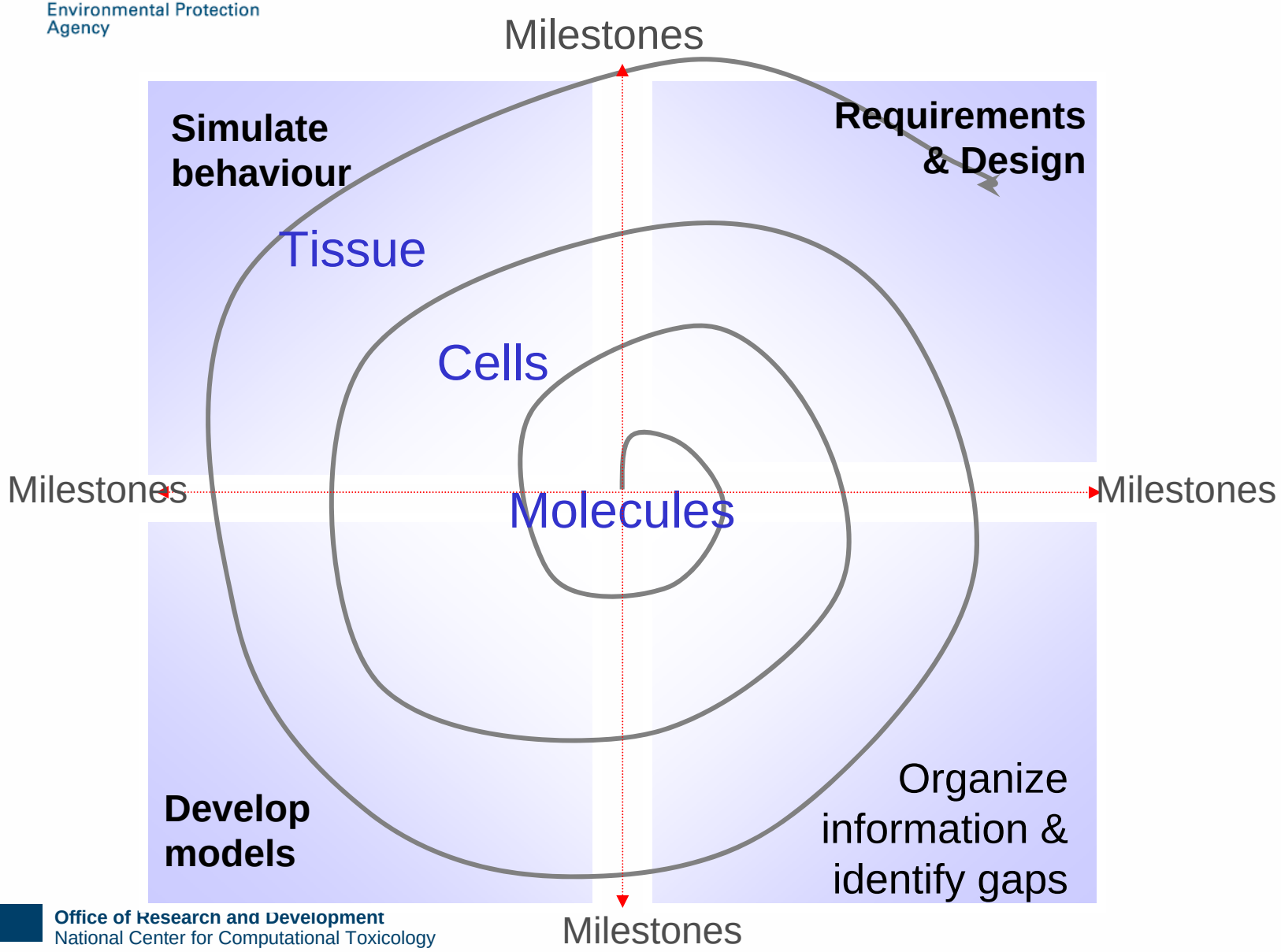
Death
- Apoptosis
- Necrosis

**Adverse Outcome**

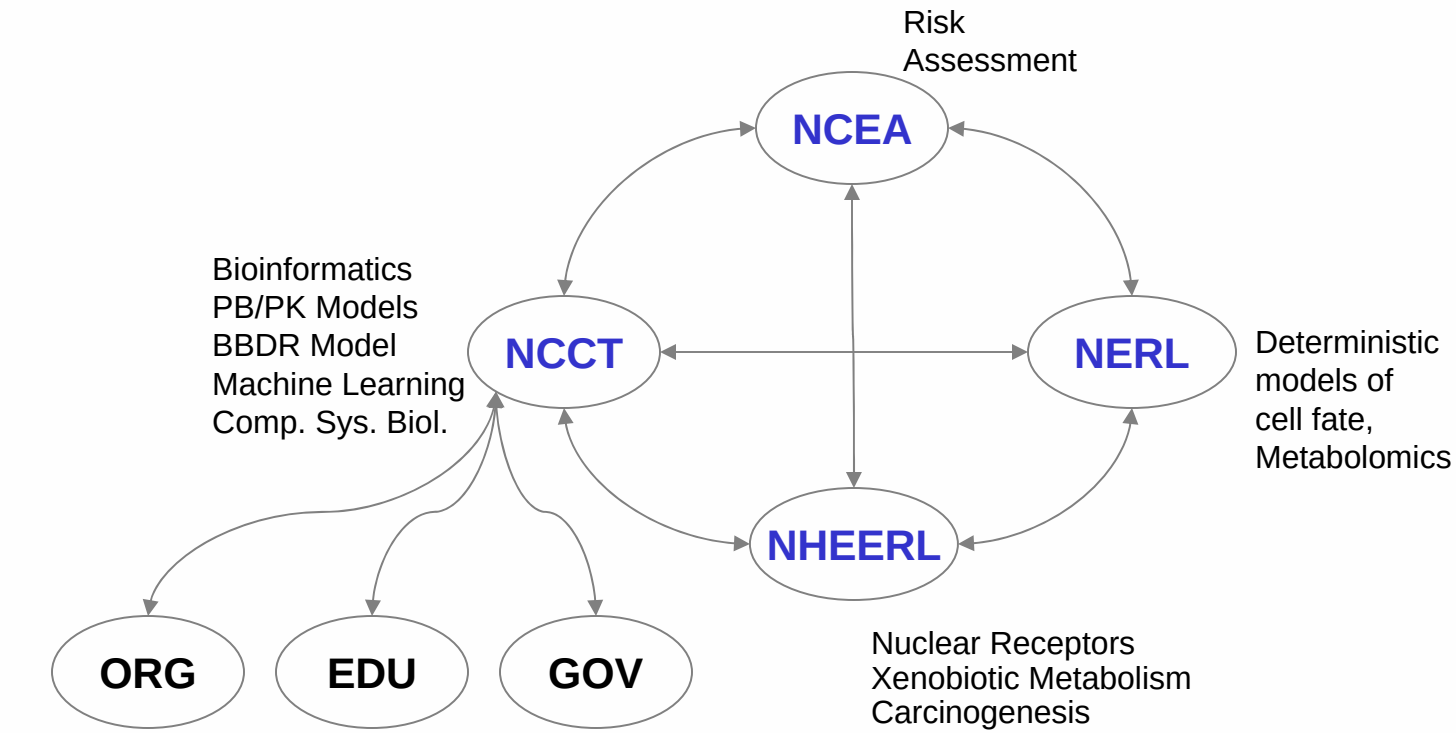
Tumor

Cancer

# Incremental Modeling Approach



# Virtual Liver Project: Multi-disciplinary Collaborative Initiatives




- **Related efforts**
  - **Physiome.org – physiological modeling (Australia)**
  - **Hepatosys.org – hepatocyte modeling (EU)**
  - **Cardiac modeling**

# Summary

- The Virtual Liver Project
  - *Tools to aid risk assessment*
  - *A new paradigm for predicting dose-response*
  - *Requires a multi-disciplinary team effort*
- Many Challenges
  - *Complexity of biological function*
  - *Knowledge representation and database development*
  - *Generating biological data to enable modeling*
  - *Multiscale dynamic simulation*
- Collaboration key to success !